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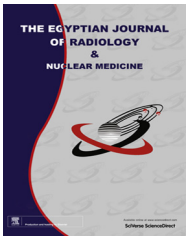

ORIGINAL ARTICLE

The diagnostic usefulness of FDG-PET/CT in detecting tumor recurrence not evident in whole body I^{131} scan in differentiated thyroid carcinoma

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Abstract *Objective:* Patients with differentiated thyroid carcinoma (DTC) have generally an encouraging prognosis, however, some patients develop an increasing level of serum thyroglobulin (Tg) without detection of a recurrent tumor using conventional imaging tools such as the iodine-131 whole-body scanning (I^{131} scan). The objective of our study was to evaluate the clinical significance of [F^{18}]-FDG-PET/CT in detection of tumor recurrence or metastases, in comparison to conventional imaging such as the I^{131} scan.

Patients and methods: Between January 2013 and June 2013, [18F]-FDG-PET/CT examination was done for 12 DTC patients with elevated thyroglobulin levels and who did not show any pathological lesions when conventional imaging modalities were used. All involved patients had undergone total thyroidectomy, and who had been followed-up by whole body iodine scan [F^{18}]-FDG PET/CT data were evaluated for detecting recurrent DTC lesions in study patients and compared with those of other radiological and/or cytological investigations.

Results: Five of 12 patients (41.6 %) showed pathological [F18]-FDG uptake in the absence of abnormal uptake in whole body iodine scan.

Conclusion: [F18]-FDG-PET/CT affords a valuable diagnostic method in detection of recurrence or metastasis in patients with DTC who are tumor-free on conventional imaging studies with high Tg levels.

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1. Introduction

Patients with differentiated thyroid carcinoma (DTC) have favorable prognosis, however, recurrence is noted in up to 30% of such patients (1). In clinical practice, measurement of serum thyroglobulin (Tg) and the I^{131} whole body scan (WBS) are the mainstays of DTC patient evaluation after treatment and during follow-up. Although the I^{131} scan has high specificity, yet some of papillary and follicular thyroid carcinoma recurrences are not avid for I^{131} uptake (2). Neck ultrasonography (US) may also be helpful in early detection of small cervical metastases as the most common site of recurrence is the cervical lymph nodes (3). However, a diagnostic dilemma is posed by patients with increased levels of Tg, in the absence of detection of recurrent cancer using conventional imaging tools such as the iodine-131 whole-body scanning or neck US. The loss of the capacity to concentrate iodine when Tg levels are elevated demands the use of imaging tools other than the I^{131} scan (4). Positron emission tomography (PET) is an advanced diagnostic imaging permitting anatomical tumor localization, the major positron emission tomography (PET) tracer in use is fluorine 18 (18F) fluorodeoxyglucose (FDG), which targets glucose metabolism in tumors. The biological target for FDG is the accelerated rate of glycolysis intrinsic to the tumor processes. PET has been used to accurately detect both iodine- and non-iodine avid recurrence. Moreover [18F]-FDG-PET is performed before considering repeated high-dose radioiodine (RI) treatment, this may render unnecessary RI, and further optimal management such as surgery or irradiation can be usefully indicated.

Although recurrent or metastatic DTC tumors grow rather slowly, such tumors consume more glucose than does normal tissue. Consequently, the use of [18F]-FDG-PET has been suggested to be valuable in patients who are negative (in terms of tumor recurrence) on conventional imaging but who show elevated Tg levels. The technique has been used to detect both local DTC recurrence and distant metastasis (5). This may increase the clinical application of such imaging modality in thyroid cancer patients because detailed anatomical information is obtained and iodine-positive tissue can be located (4).

The aim of our study was to evaluate the utility of [18F]-FDG-PET/CT in detection of recurrent DTC in patients with increasing serum Tg levels who showed no pathological finding upon conventional imaging modalities such as cervical US and the I^{131} scan.

2. Materials and methods

Between Jan 2013 and June 2013, 12 patients with histologically proven DTC were enrolled in our study. All patients had previously undergone total thyroidectomy and all patients showed increasing pathological Tg levels (Tg > 9–10 ng/mL) after TSH stimulation (TSH > 30 mU/L). However, neither tumor recurrence nor metastasis could be detected in any patient by post-therapeutic I^{131} scan, neck US, or chest radiography. Patients with obvious cervical pathology in US or positive fine-needle aspiration cytology (FNAC) were excluded from the study.

2.1. Study protocol

(1) Blood and urine samples were collected for routine examination; to measure blood TSH, Tg, and anti-Tg antibody levels; and to assess urine iodine excretion after 4 weeks of levothyroxine withdrawal. All patients had consumed a low-iodine diet for the prior 2 weeks, following written instructions and assisted by a dietician.
(2) A I^{131} scan was obtained 72 h after administration of 2–4 mCi of I131 using a Philips Bright view dual headed scanner and patients with negative scan were asked to perform a [18F]-FDG PET/CT.
(3) Patients fasted for at least 4 h before PET/CT examination, and were (intravenously) given 370 MBq [18F]-FDG. All patients were instructed to rest comfortably for 60 min and to empty the bladder before scanning. Whole-body PET/CT images were obtained using a Ingenuity, TF PET/CT /Philips. Seven or eight frames (3 min/frame) of emission PET data were acquired in the two-dimensional mode after low dose non-contrast CT scans had been performed from the base of the skull to the mid thigh (tube rotation time of 1 s per revolution; 120 kV; 60 mA; 7.5 mm per rotation; and an acquisition time of 60.9 s for a scan length of 867 mm). Attenuation corrected PET/CT images were reviewed on a Philips workstation. All images were independently interpreted by two experienced physicians and screened for "overactive uptake" indicative of functioning thyroid tissue on I^{131} scan and standardized uptake value (SUV) more than 3.2 is considered as hyper metabolic abnormalities on PET/CT.

3. Results

Findings on [18F]-FDG-PET were compared with data from diagnostic whole body I^{131} scans. Moreover, the data were compared with those of radiological imaging (US, CT, and MRI information), and/or those of cytological investigation (FNAC), to confirm (or otherwise) the findings of the I131 scans, and those of PET/CT (using [18F]-FDG). For each patient, the presence or absence, and number and localization of any recurrent lesions (if present) were determined. PET/CT scans findings were considered positive, if there is hypermetabolic uptake with SUV max > 3.2.

The characteristics of the 12 patients included in our study are showed in Table 1. The demographic distribution included 3 male patients (25%) and 9 female patients (75%).

Five of our 12 patients had areas of abnormal FDG uptake inspite of negative whole body iodine scan, they were classified based on the anatomical distribution of F18 FDG metabolically active lesions into 3 patients had recurrent hypermetabolic cervical lymphadenopathy, one patient had hypermetabolic mediastinal lymphadeopathy with lung metastases (Fig. 1) and one patient had hypermetabolic peritoneal nodule only (Fig. 2).

Table 1 Patients characteristics and radiological findings.

Patients No.	Sex	Age	Pervious RI dose (mCi)	Tg (ng/mL)	TSH	I^{131}	Other imaging modalities	F18-FDG PETCT
1	M	60	80	22.4	89	−Ve	−Ve	**+ve**
2	F	35	100	11.1	55	−Ve	−Ve	−Ve
3	F	41	75	19.2	60	−Ve	−Ve	−Ve
4	F	22	87	30	31	−Ve	−Ve	**+ve**
5	M	27	88	16.2	48	−Ve	−Ve	−Ve
6	F	39	77	10.9	98	−Ve	−Ve	−Ve
7	F	49	120	21	90	−Ve	−Ve	−Ve
8	M	51	89	63.3	78	−Ve	−Ve	**+ve**
9	F	32	90	70.1	63	−Ve	−Ve	**+ve**
10	F	70	105	17.1	56	−Ve	−Ve	−Ve
11	F	44	100	44.2	130	−Ve	−Ve	−Ve
12	F	59	100	91.5	100	−Ve	−Ve	**+ve**

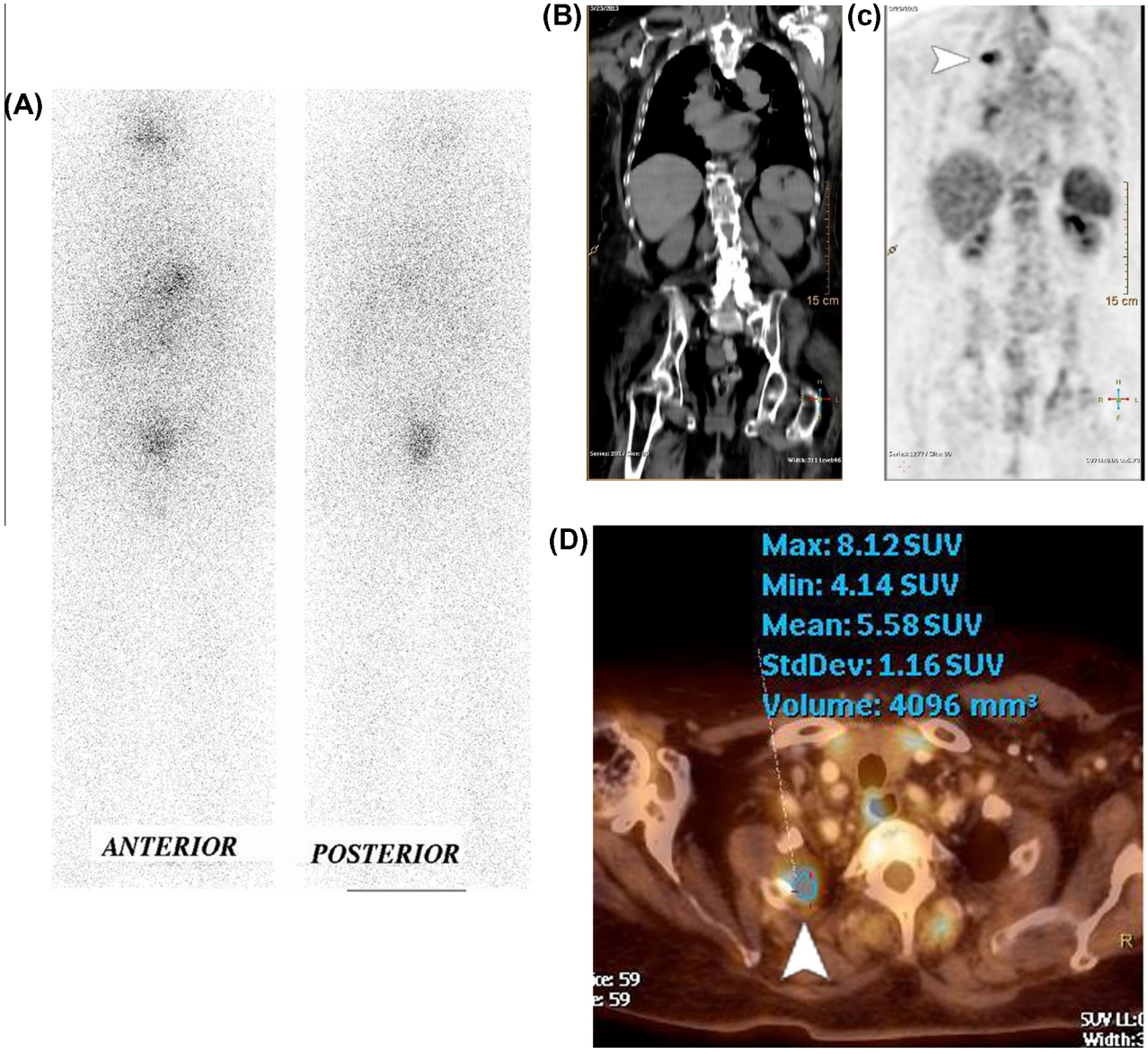

Fig. 1 48 year old female patient presented with history of papillary thyroid cancer treated by subtotal thyroidectomy followed by ablative dose of radioactive iodine (100 mCi); on follow up despite negative I^{131} whole body scan (A) for any residual, recurrent functioning thyroid tissue or distant metastases, yet the Tg was remarkably elevated, PET (C) and PET/CT (D) revealed increased avidity of 18F-FDG uptake at the right lung (arrow heads) not evident in corresponding conventional CT image (B).

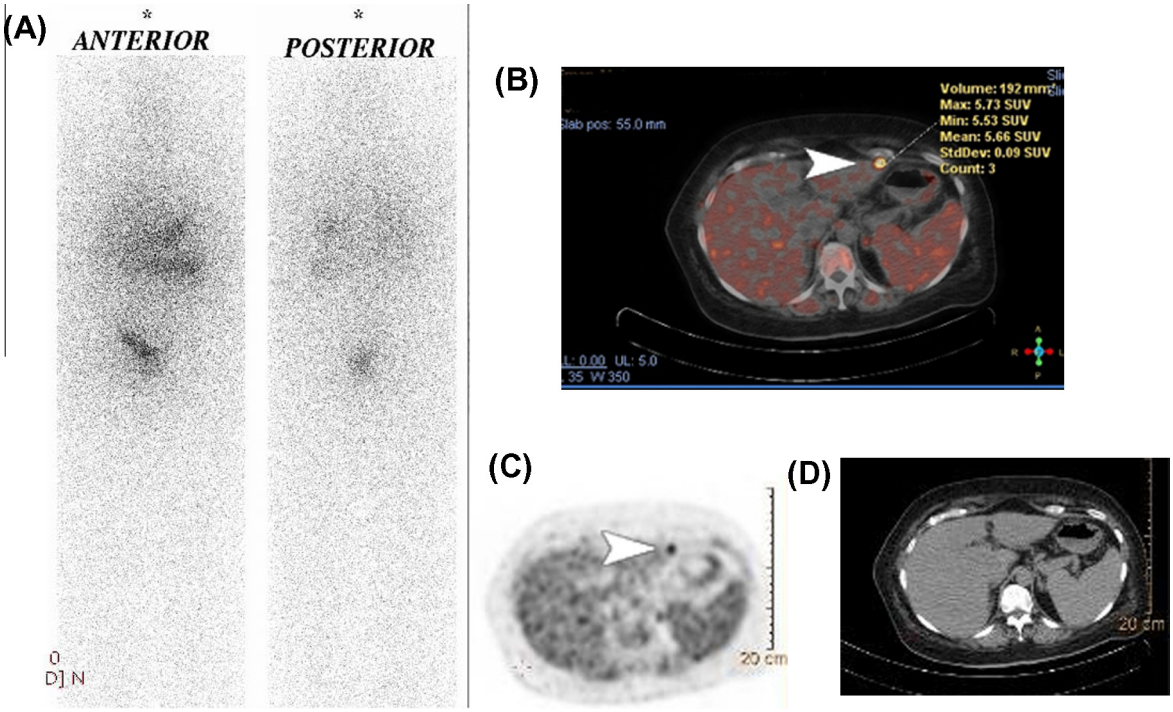

Fig. 2 A male patient 52 year old presented with history of papillary-follicular thyroid cancer treated by total thyroidectomy followed by large dose radioactive iodine therapy; the thyroglobulin level showed progressively increased titer on follow up in spite of −ve whole body iodine scan (A) while PET/CT and PET showed distant metastases in the form of small hypermetabolic peritoneal deposit (arrow heads) with SUV max measured 5.73 (B and C) not seen on conventional CT (D).

4. Discussion

These are the results of our study on the use of PET/CT using [18F]-FDG to locate recurrent DTC lesions in patients with elevated thyroglobulin levels with no pathological lesions detected by conventional imaging modalities. Our study showed that the use of [18F]-FDG-PET/CT revealed the complete extent of the disease and afforded precise anatomical localization of recurrent lesions in 5 out of 12 patients (41.6%). Thus, performing [18F]-FDG-PET/CT before high-dose RI treatment was considered, would facilitate diagnostic accuracy and might avoid unnecessary exposure of patients to radiation.

Empirical high-dose RI treatment may be indicated in patients with increased levels of Tg in the absence of pathological lesions detected by conventional imaging tests (the I^{131} scan, neck US, and/or chest radiography) followed by a post-treatment I^{131} scan. However, repeated empirical treatment with RI may unnecessarily expose patients to high levels of radiation; this may be a particular problem in patients who show no I^{131} uptake on the post-treatment scan (5). Therefore, an advanced diagnostic imaging technique providing accurate anatomical localization, such as [18F]-FDG-PET/CT, is required. The information provided by such scans is necessary to allow physicians to accurately locate metastatic lesions and to indicate the most efficient therapeutic options.

In the past years, SUV max of 2.5 was considered by many studies as a cut off value to differentiate benign and malignant tumors, however, in countries where the incidence of infectious and inflammatory disease is higher, this cut off value does not work and a significantly higher SUV is noted in infections and inflammation (6).

In our study, we used SUV max of 3.2 as a cut off value for detecting malignancies as also recommended by Wong et al. (7), who found that using this cut off value yielded a sensitivity of 92% and specificity of 70% for recurrent head and neck malignancies, similar cut off value is used by Takeda et al. (8), who stated that SUV max of 3.2 showed sensitivity of 100% and sensitivity of 96% for detecting recurrence of localized non small cell carcinomas. Huang et al. (9), showed that the same SUV max is the cut off value to predict tumor control of HCC after ablative radiotherapy, also Ergul et al. (10), showed that cut off of 3.2 obtained the most effective sensitivity and specificity in the diagnosis of pancreatic cancer. While Wafaie et al. (11), used SUV max of 3 as a cut off value for detecting malignant osseous lesions, Meteser et al. (12), used SUV max of 3.1 to detect malignant adrenal tumors, Choi et al. (13) used SUV max of 3 as a cut off value for detecting recurrence of papillary thyroid carcinoma.

In our patient series, PET/CT using [18F]-FDG was more accurate in terms of lesion localization than was conventional imaging in 5 of our 12 patients (41.6%). Currently, [18F]-FDG-PET/CT is recognized as useful in examination of DTC patients who present with negative I^{131} scan data but pathologically increased Tg levels (5) Moreover, any difference between PET findings and conventional I^{131} scan information can provide important clinical clues relevant to treatment of recurrent DTC.

Some authors have reported that TSH elevation increases [18F]-FDG uptake in DTC patients experiencing recurrence and seems to improve PET/CT scan sensitivity. In such patients, the value of hormonal stimulation by TSH is great as small sized or low metabolic activity lesions become apparent

(14). However, other reports found no increase in the accuracy (sensitivity) of scan data obtained after hormonal TSH stimulation (15). Accordingly, no consensus on the effect of TSH stimulation on FDG-PET accuracy has been attained and it is important to render scanning cost-effective (5).

In clinical practice, RI treatment of patients with negative low dose diagnostic I^{131} scan but with elevated Tg levels has been used diagnostically, therapeutically, and assessment of prognosis (16). In addition, patients who show no iodine accumulation on post-treatment I^{131} scanning (which may indicate tumor dedifferentiation) have a poorer prognosis than do others (17).

Seven of our 12 patients showed no abnormality in PET/CT although having high levels of increased thyroglobulin. They were managed according to the American thyroid association (18) which recommended that empiric radioactive iodine therapy (100–200 mCi) might be considered in patients with elevated thyroglobulin (thyroglobulin levels after T4 withdrawal of 10 ng/ml or higher, or a level of 5 ng/ml after TSH stimulation) or rising serum levels of thyroglobulin in whom imaging failed to reveal a potential tumor source.

Our study had some limitations. Our patient number was small and large prospective investigations are needed to support our data. Second our follow-up period was relatively short and longer periods are needed to establish statistically reliable data.

In conclusion [18F]-FDG PET/CT is a useful diagnostic tool when recurrence occurs in DTC patients who have elevated Tg levels but no definitive abnormalities by conventional imaging.

Conflict of interest

None declared.

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